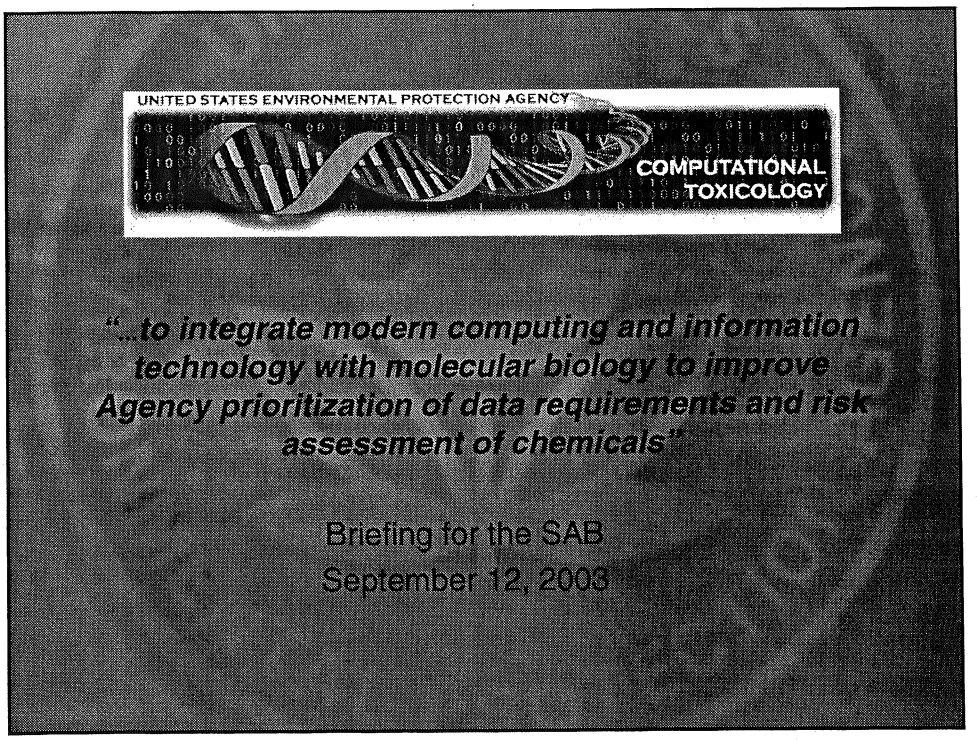

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Historical Perspective

- FY02 Congressional re-direction to provide funds for non-animal alternative testing
- FY03 effort continued to use endocrine disruptors as proof-of-concept activity
- Leadership by Paul Gilman, AA for ORD, to increase emphasis on Computational Toxicology within EPA

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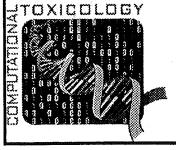

ORD Technical Design Team

- Formed in late 2002
- Consists of representatives from five ORD Labs/Centers
- Charged with drafting Framework for a Computational Toxicology Research Initiative within ORD
- Development of a Research Strategy in Computational Toxicology is an Annual Performance Measure in FY04

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ORD Design Team

NCEA	NCER	NERL	NHEERL	NRMRL
K. Hammerstrom	E. Francis	J. Blancato	G. Ankley	D. Young
J. Swartout		T. Collette	J. Fowle	
		G. Toth	E. Gray	
		E. Weber	R. Kavlock	
			H. Tilson	
			G. Veith	
			D. Wolf	

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Overarching Themes

- A technology-based, hypothesis-driven effort to increase the soundness of risk assessment decisions within EPA
- Build the capacity to prioritize, screen and evaluate chemicals by enhancing the predictive understanding of toxicity pathways
- Success measured by ability to produce faster and more accurate risk assessments for less cost relative to traditional means and to classify chemicals by their potential to influence molecular and biochemical pathways of concern

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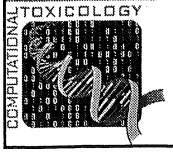
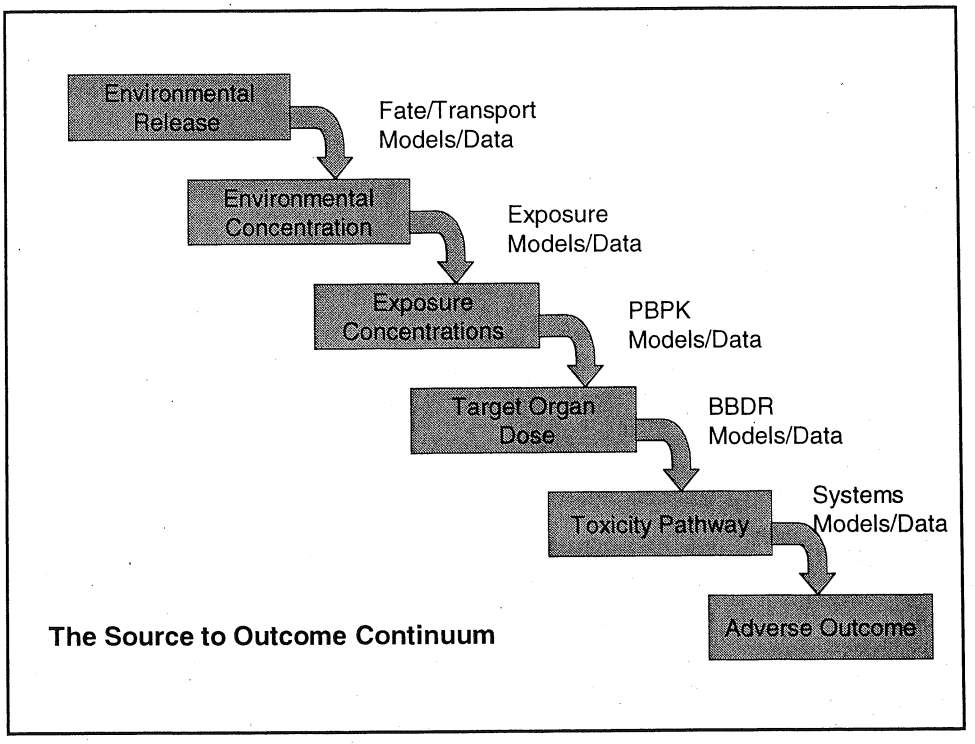


General Objectives

I. Improve linkages in the source-to-outcome paradigm

II. Provide predictive models for screening and testing

III. Enhance quantitative risk assessment



The Source to Outcome Continuum

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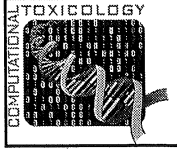

I. Source to Outcome Linkages

- ❑ Chemical transformation and metabolism
- ❑ Diagnostic/prognostic molecular indicators
- ❑ Dose metrics
- ❑ Characterization of toxicity pathways
- ❑ Metabonomics
- ❑ Systems biology

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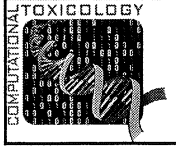

II. Predictive Models for Hazard Identification

- QSAR approaches
- Pollution prevention strategies
- High throughput screening

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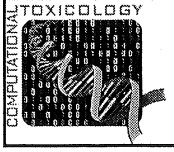

III. Enhancing Quantitative RA

- Applying computational methods in quantitative risk assessments
  - Validation and development of protocols
  - Defining responses
  - Modifying Uncertainty factors
- Dose response assessments
- Cross species extrapolations
- Chemical mixtures

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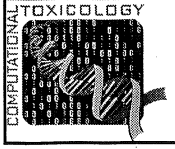

EDC Proof of Concept

- Receptor binding models
- Thyroid hormone pathways
- Steroidogenesis
- Hypothalamic-pituitary axis

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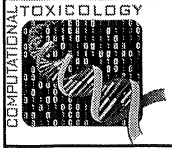

CompTox Activities

- Infrastructure building
  - ORD Capital Equipment Committee
    - Affymetrix platform (NHEERL)
    - Wide-bore 600 MHz NMR (NERL)
  - NGPC
- Partnership development
  - DOE/JGI - fathead minnow, Xenopus sequencing
  - DOE/Sandia
  - NIEHS/NCT – CEBS database, NAS Workgroup
  - CIIT Centers for Health Research
- STAR RFAs
  - High throughput screening systems (FY03)
  - Neuroendocrine system models (open until 1/04)
- SAB Consult, Sept. 12, 2003
- ORD Workshop, Sept. 29-30, 2003

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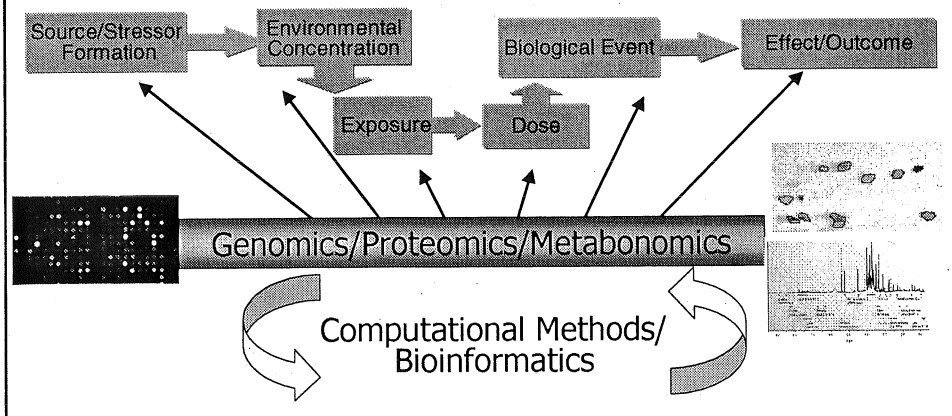
CompTox Workshop:

Research Framework, Partnerships and Program Development

- Introduction to the Framework
- Related research strategies from other organizations
- Highlighted approaches
  - Diagnostic indicators, high throughput screening, toxicity pathway identification, metabonomics and systems biology
- Regulatory needs
  - OPPTS, OPP, FDA
- Breakout group discussions
  - "top down" and "bottom up"



Integrate molecular biology and chemistry to prioritize data requirements and to improve risk assessment

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Computational Toxicology

Prediction
Prioritization
Quantitative Risk Assessment

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The Future

- Planning
  - Incorporate inputs from the Consult and the Workshop
  - Produce and distribute a Workshop summary
  - Coordinate with the EPA Genomics Task Force
  - Implementation Team to begin identifying specific areas for program development
- Budget
  - FY04 request includes realigned and redirected base resources from FY02/03 and additional resources to extend proof-of-concept to other chemicals
  - FY05 request to expand approach to pesticidal inerts and to non-pesticidal anti-microbials
  - Complement intramural activities with STAR program, including potential Center for Bioinformatics

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Performance Measures

- Research Outputs
  - Libraries of toxicity pathways
  - Characterization of metabolic activation pathways
  - Biologically based predictive models
- Programmatic Outputs
  - Predictive models to prioritize chemicals for testing
  - Improve efficiency in risk assessment
  - Reduce cost to evaluate chemical risks
  - Reduce dependency on animal testing
  - Reduce risk to public health and the environment